Targeted Filgrastim Support in Patients with Early-Stage Breast Carcinoma

Toward the Implementation of a Risk Model

Edgardo Rivera, M.D.[1]
M. Haim Erder, Ph.D.[2]
Timothy D. Moore, M.D.[3]
Thomas L. Shiftan, M.D.[4]
Chris A. Knight, M.D.[5]
Moshe Fridman, Ph.D.[6]
Carol Brannan, R.N.[2]
Laurence Danel-Moore, M.D.[2]
Gabriel N. Hortobagyi, M.D.[1]
for the Risk Model Study Group

[1] Department of Breast Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston, Texas.

[2] Amgen Incorporated, Thousand Oaks, California.

[3] Mid-Ohio Hematology Oncology, Columbus, Ohio.

[4] Sidney Kimmel Cancer Center, San Diego, California.

[5] Forum Health, Youngstown, Ohio.

[6] AMF Consulting Incorporated, Los Angeles, California.

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Additional members of the Neutropenia Risk Model Study Group include: Mitchell Alden, M.D., Bux-Mont Oncology/Hematology Medical Associates, Sellersville, PA; Francis P. Arena, M.D., Arena Oncology Associates, Great Neck, NY; John A. Axelson, M.D., Hematology/Oncology Association of Southern Michigan, Jackson, MI; Suzanne T. Berlin, M.D., Addison-Gilbert Hospital, Gloucester, MA; Stephanie Bernstein, M.D., Faulkner Hospital, Jamaica Plains, MA; Rachel Borson, M.D., Midwest Cancer Center, St. Louis, MO; Albert M. Brady, M.D., St. Joseph Mercy Oakland, Pontiac, MI; Michael S. Buchholtz, M.D., Hematology/Oncology, Huntington, NY; Janak E. Choksi, M.D., Alamance Cancer Center, Burlington, NC; Patrick Colarusso, M.D., Pottstown Memorial Cancer Center, Pottstown, PA; Elliot Dickman, M.D., Hillcrest Hospital Cancer Center, Mayfield Heights, OH; David Dunning, M.D., Northern Virginia Oncology Group, Fairfax, VA; Leroy J. Essig, M.D., Medical Specialists of Fredericksburg, Fredericksburg, VA; Frank J. Forte, M.D., Staten Island University Hospital, Staten Island, NY; Julio M. Garcia, M.D., Oncology/Radiation Associates, Miami, FL; Jeremy R. Geffen, M.D., Geffen Cancer Center, Vero Beach, FL; Charles D. Graham, M.D., Trident Palmetto Hematology/Oncology, Charleston, SC; Andrew A. Hertler, M.D., Maine General Health, Waterville, ME; Karen L. Hoelzer, M.D., Springfield Clinica, Springfield, IL; Anthony D. Hoffman, M.D., Sciode Medical Association, Bronx, NY; Leonard A. Kalman, M.D., Oncology/Hematology Group of South Florida, Miami, FL; Edward H. Kaplan, M.D., North Shore Cancer Research, Skokie, IL; Joseph Kaplan, M.D., Community Hematology/Oncology, Olney, MD; Kapisthalam S. Kumar, M.D., Pasco Hernando Oncology Associates, New Port Richey, FL; Steven S. Larmon, M.D., Dartmouth-Hitchcock Hospital, Keene, NH; James J. Lechner, M.D., Western Washington Oncology, Olympia, WA; William A. Lerner, M.D., Topilow, Lerner & Mencel, Manasquan, NJ; James E. Liebmann, M.D., New Mexico Oncology/Hematology Consultants, Albuquerque, NM; Robert J. March, M.D., Hematology/Oncology Associates, New City, NY; Leslie A. Martin, M.D., St Elizabeth's Medical Center, Brighton, MA; Edward T. O'Brien, M.D., The Regional Cancer Center, Erie, PA; John A. Okerbloom, M.D., Heartland Oncology & Hematology, Council Bluffs, IA; James M. Orsini, M.D., Essex Hematology/Oncology Group, Belleville, NJ; Stuart H. Packer, M.D., Hematology/Oncology, Langhorne, PA; Sigurdur R. Petursson, M.D., Western Pennsylvania Hospital, Pittsburgh, PA; Debra M. Prow, M.D., Texas Cancer Center, Fort Worth, TX; Jane M. Raymond, M.D., Western Pennsylvania Hospital, Pittsburgh, PA; Joseph A. Readling, M.D., Lourdes Regional Cancer Center, Binghamton, NY; Joel H. Schwartz, M.D., North Shore Cancer Center, Peabody, MA; David Shiba, M.D., Gould Medical Group, Modesto, CA; Michael J. Stender, M.D., Hematology/Oncology Consultants, Royal Oak, MI; N. Simon Tchekmedyian, M.D., Pacific Shores Medical Group, Long Beach, CA; Kathleen Toomey, M.D., Somerset Hematology/Oncology, Somerset, NJ; Dean Tsarwhas, M.D., North Shore Oncology/Hematology, Libertyville, IL; Stephen A. Volk, M.D., Oncology/Hematology of Lehigh Valley, Bethlehem, PA; Pivapong Vongkovit, M.D., Northwestern Carolina Oncology/Hematology, Hickory, NC; and Marjorie A. Vukelich, M.D., Kettle Moraine Oncology, West Bend, WI.

BACKGROUND. Severe neutropenia, a common consequence of chemotherapy, may result in infectious complications and hospitalizations. Preventive treatment with colony-stimulating factors is limited because of the inability to predict which patients will develop neutropenic complications. To the authors' knowledge, the current study is the first large prospective validation of a risk model in patients with early-stage breast carcinoma.

METHODS. Patients with Stage I–III breast carcinoma who were receiving adjuvant chemotherapy ($n = 624$) were assigned to risk groups based on first-cycle absolute neutrophil count (ANC) nadirs of $< 0.5 \times 10^9$/L. Filgrastim (a recombinant human granulocyte–colony-stimulating factor) was administered from Cycle 2 onward to high-risk patients. Dose intensity and rates of neutropenic complications, including febrile neutropenia and hospitalization resulting from it, were calculated for each group and compared. High-risk patients were matched by chemotherapy

Address for reprints: Edgardo Rivera, M.D., University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Unit 424, Houston, TX 77030-0056; Fax: (713) 794-4385; E-mail: erivera@mail.mdanderson.org

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regimen, stage of disease, age, and baseline ANC to historic-control patients and outcomes were compared within the matched pairs.

RESULTS. Both risk groups were found to have a similar proportion of patients receiving > 85% of the dose intensity (95.8% vs. 94.4%). The rate of febrile neutropenia and hospitalization in the low-risk group (n = 264) was 2.6% (95% confidence interval [95% CI[], 0.7–4.5%) and 0.8 (95% CI, -0.3–1.9%), respectively. The high-risk group was 2.6 times more likely to receive a full dose of chemotherapy, but no higher risk of neutropenic complications was reported compared with the matched controls.

CONCLUSIONS. The risk-related prophylactic administration of filgrastim facilitated the delivery of planned chemotherapy to the high-risk group of patients. However, further research is needed to confirm the results obtained in the current study in a randomized trial, if feasible, and in other chemotherapy and disease settings. ***Cancer*** **2003;98:222–8.** © *2003 American Cancer Society.*

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Breast carcinoma is the most common cancer in women in the U.S., with 205,600 new cases and 40,000 deaths expected to be reported for 2002.[1] The current standard of care for patients with early-stage breast carcinoma, which accounts for nearly 67% of all new diagnoses of breast carcinoma,[2] is comprised of breast-conserving surgery, local radiation therapy, hormonal therapy, and systemic adjuvant chemotherapy.[3] The survival benefit conferred by the timely administration of full-dose adjuvant chemotherapy is well established.[4–7] Not all patients with early-stage breast carcinoma receive their planned dose of chemotherapy on time. Dose reductions and delays are fairly common in the treatment of patients with early-stage breast carcinoma, primarily because of neutropenic complications. A retrospective, multicenter, oncology practice pattern study found that, overall, 70% of women received ≥ 85% of the average dose intensity relative to the corresponding standard regimen and 78% received > 85% average dose intensity relative to the initially planned dose intensity.[8] Neutropenia-related reasons accounted for 58% of all cycle delays and for 53% of all dose reductions in this study. In another survey (n = 20,000), nearly 80% of the patients received > 85% of their initially planned dose intensity, and these rates were lower for elderly patients (67%).[9] A Canadian retrospective multicenter study found that 42% of the patients receiving adjuvant chemotherapy for breast carcinoma experienced at least one neutropenic complication, defined as an episode of febrile neutropenia, dose reduction, or dose delay because of neutropenia.[10] The idea that chemotherapy dose delays and reductions are an acceptable choice of care in the adjuvant setting appears to be supported by current American Society of Clinical Oncology guidelines for the use of colony-stimulating factors; the guidelines suggest that physicians consider chemotherapy dose modifications as the primary response to the risk of hematologic toxicity in patients with early-stage breast carcinoma.[11]

Primary prophylaxis with colony-stimulating factors is an alternative method for reducing the risk of neutropenic complications without resorting to chemotherapy dose modifications. The prophylactic use of filgrastim (a recombinant human granulocyte–colony-simulating factor [rHuG-CSF]) reduces the risk of hematologic complications and helps maintain the planned dose on time.[12–15] filgrastim support, given as primary prophylaxis, is offered to only 3% of patients. However, approximately 45% of patients experience dose delays and/or dose reductions.[8] Primary prophylactic use of filgrastim has been limited partly because it was impossible to predict which patients were at risk for neutropenic complications and chemotherapy modifications, making the prophylactic use of filgrastim costly if administered indiscriminately to all patients. The development of reliable models capable of ranking patients by the risk for neutropenic complications may facilitate the efficient targeting of filgrastim treatment to high-risk patients.

Silber et al.[16] developed and retrospectively validated a model predicting patients' risk for febrile neutropenia, severe neutropenia, and dose reduction or delay based on the first-cycle absolute neutrophil count (ANC) nadir in women treated with adjuvant chemotherapy for early-stage breast carcinoma. Studies analyzing additional chemotherapy regimens have since confirmed the value of the first-cycle ANC nadir as a predictor of neutropenic complications in patients receiving adjuvant chemotherapy for early-stage breast carcinoma.[17,18] Silber et al.[19] argued that using the first-cycle ANC nadir to target filgrastim use based

on risk to the 50% of patients at highest-risk was cost-effective and comparable to the cost for the treatment of other common medical conditions.

In the current study, we took the first steps toward the prospective implementation of the findings by Silber et al.[16] First-cycle ANC nadir was used to guide risk-related prophylactic filgrastim treatment to the neediest patients. Successful implementation of this model should allow those patients at low risk of developing neutropenic complications to receive full-dose chemotherapy on time with minimal neutropenic complications without the use of filgrastim and allow patients at high risk of developing neutropenic complications to receive the same dose intensity as patients in the low-risk group. The incidence of neutropenic complications in the high-risk group should not be substantially greater than that observed in common practice. The purpose of this study was to test our hypotheses concerning the delivery of a full dose of chemotherapy on time to the high-risk and low-risk groups and the hypothesis that the low-risk group would have minimal neutropenic complications in the absence of filgrastim support. Confirmation of these results would set the stage for a randomized study evaluating the net increase in dose intensity when filgrastim is used as prophylaxis and the resulting incidence of neutropenic complications due to the dose increase. We also compared the incidence of neutropenic complications in the high-risk group with a matched historic control group to obtain a preliminary estimate of the incidence of neutropenic complications relative to common practice.

MATERIALS AND METHODS

Patients

The study protocol was reviewed and approved by the institutional review board at each participating center, and written informed consent was obtained from all patients before any study-related procedures were performed. Patients were enrolled consecutively at 75 diverse, primarily community-based sites between 1999–2000. Patients were eligible for the study if they were age $\geq$ 18 years with newly diagnosed, resected, and histologically confirmed AJCC/TNM Stage I-III breast carcinoma and had not received chemotherapy or radiation therapy within the previous 2 years. A leukocyte count $> 4.0 \times 10^9$/L, a platelet count $> 150 \times 10^9$/L, and adequate renal (creatinine $<$ 1.5 times the upper limit of normal) and hepatic (alanine aminotransferase or aspartate aminotransferase levels $\leq$ 2.5 times the upper limit of normal) function were required at study entry. Patients with active infection requiring intravenous or oral antibiotics were excluded, as were women who were pregnant or breast-feeding.

Study Design

This study was prospective, open-label, and nonrandomized, a design chosen to explore the feasibility of implementing the risk model while minimizing the risk to patients. Patients could be treated with the following chemotherapy regimens: doxorubicin and cyclophosphamide (AC); cyclophosphamide, methotrexate, and 5-fluorouracil (CMF); cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF); or doxorubicin followed by CMF (A–CMF), using standard regimens. The first cycle of chemotherapy was administered without filgrastim support.

To be eligible for the study and to ensure proper risk-group assignment, study patients were required to have 2 complete blood counts with differential drawn at least 3 days apart between Days 8–15 of Cycle 1 and before any administration of filgrastim; a third complete blood count was drawn on Day 22 for regimens with a 28-day chemotherapy cycle. The first-cycle ANC nadir was defined as the lowest of these counts.

Patients were assigned to low-risk or high-risk groups based on their first-cycle ANC nadir ($> 0.5 \times 10^9$/L and $\leq 0.5 \times 10^9$/L, respectively) because it was expected to split the sample into approximately equal-sized risk groups. However, because the depth of first-cycle neutropenia varies with the toxicity of the chemotherapy regimen and with other factors, it is difficult to predict an exact single cut point that would split a multiregimen sample. In the high-risk group, prophylactic filgrastim support was given beginning with the second cycle of chemotherapy and continuing through the last cycle of chemotherapy. Filgrastim support was given to patients in the low-risk group only if there was delayed hematologic recovery or if the patient had an episode of febrile neutropenia (temperature $>$ 38.3 °C and ANC $\leq 0.5 \times 10^9$/L), and prophylactic filgrastim was continued in all remaining chemotherapy cycles. Filgrastim at a dose of 5 μg/kg/day was administered subcutaneously to patients in the high-risk group beginning 24 hours after the completion of the chemotherapy cycle and continuing until the ANC reached $\geq 10.0 \times 10^9$/L. Hematologic recovery was defined as a platelet count $\geq 100 \times 10^9$/L and either a leukocyte count $\geq 3.0 \times 10^9$/L or an ANC $\geq 1.5 \times 10^9$/L. For all study patients, if recovery did not occur by the scheduled start of a subsequent chemotherapy cycle, that cycle was delayed until the counts recovered. Once hematologic recovery occurred, the delayed chemotherapy was administered at full dose with filgrastim support. In the event of a

second delay in hematologic recovery, the chemotherapy dose could be reduced by up to 25% at the discretion of the investigator. A third delay in hematologic recovery prompted a 25–50% reduction in the dose of chemotherapy, also at the investigator's discretion.

The historical-control group was identified from retrospective data collected for an Oncology Practice Pattern Study conducted at 14 large, managed-care, academic, integrated hospital systems and community practices across the U.S. between 1993 and 1999.[8] The control group was comprised of 1022 patients with early-stage breast carcinoma who were treated with AC, CMF, CAF, or A-CMF adjuvant chemotherapy. Patients were eligible if they received adjuvant chemotherapy for early-stage (i.e., Stage I, Stage II, or Stage III) breast carcinoma within 3 years of study initiation, and were at least 18 years of age. Patients were excluded if they were enrolled in another clinical research protocol, had other primary invasive tumors, received a previous course of chemotherapy within 3 years of the course studied, or were pregnant or breastfeeding. The medical records were abstracted using a standardized clinical report form, under the supervision of the site principal investigator. Historic-control patients who received colony-stimulating factors as prophylaxis during the first cycle (3%) were excluded.

Study Endpoints

The primary endpoints of the current study were the proportion of patients receiving at least 85% of the planned chemotherapy dose on time, the proportion of patients hospitalized because of febrile neutropenia, and the proportion of patients experiencing an episode of febrile neutropenia. Planned dose on time was calculated for each patient by averaging the percentage of the planned dose intensity of each agent delivered in the regimen. The dose intensity delivered to each patient was calculated over the entire regimen.

Statistical Methods

Baseline characteristics and study endpoints for the current study patients prospectively assigned to the low-risk and high-risk groups were compared. The incidence of hospitalization because of febrile neutropenia and febrile neutropenia in the low-risk group was reported and tested for difference from zero, the rate expected under a perfect risk-group assignment rule. These rates are the false-negative rates (type I error) of our classification rule. The rate of low ($\leq$ 85%) delivered dose intensity (relative to the planned regimen) was estimated by risk group and the difference in rates was tested. Patients in the high-risk group were matched one to one with historic-control patients according to chemotherapy regimen, stage of disease, age, and ANC before the administration of chemotherapy. We could not classify historic-control patients into risk groups because first-cycle nadir ANC was not reported for the control-group patients. Therefore, we conservatively matched the high-risk patients to the entire historic-control sample. Regimen and stage were perfectly matched whereas study and control patients with minimal differences in age and baseline ANC were paired using an optimization procedure. Insufficient historic-control patients were available for one to two matches under the regimen and stage equivalence requirement. No access to data concerning dose intensity or the occurrence of febrile neutropenia outcomes was permitted when matching study patients with historic-control patients. Estimated odds ratios (odds of the outcome in the historic-control patient relative to the odds in the high-risk patient within a matched pair) were reported and their significance was tested using the McNemar test.[20] Two-sided Student *t* tests were used to compare continuous variables and continuity-adjusted chi-square tests were used to compare categoric variables. All reported *P* values were two-sided. Statistical analyses were performed using SAS 8.00 for Windows (SAS Institute Inc, Cary, NC).

RESULTS

Patient Demographics

A total of 672 patients were enrolled in the current prospective study. Of these, 48 patients were missing the first-cycle ANC nadir and were, by protocol definitions, ineligible for the study. Characteristics of the high-risk and low-risk groups for 624 patients are reported in Table 1. Study patients in the high-risk group had a lower baseline ANC compared with patients in the low-risk group ($P < 0.001$). Among the AC-treated and CAF-treated patients, 64% and 63%, respectively, were assigned to the high-risk group compared with 12% of the CMF-treated patients ($P < 0.001$). No difference in age group ($\geq$ 60 vs. $<$ 60 years) was found between risk groups (28.3% vs. 24.7%, older patients in high-risk vs. low-risk groups, respectively).

Older patients were more likely to receive the CMF regimen (20.5% vs. 8.9%). By protocol, all high-risk patients received prophylactic filgrastim from Cycle 2 onward. Approximately 21% of low-risk patients received secondary filgrastim for a total of 139 of 1202 cycles of chemotherapy (11.6%), primarily for low ANC and delayed hematologic recovery (data not shown).

TABLE 1
Baseline Clinical Characteristics of Patients in the High-Risk and Low-Risk Groups

Characteristic	Overall $n = 624$	High-risk patients $n = 360$	Low-risk patients $n = 264$
Age (years), mean (SD)	53.6 (11.0)	53.7 (10.9)	53.5 (11.0)
Body surface area (m^2), mean (SD)	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)
Baseline ANC ($\times 10^9$ /L), mean (SD)	4.4 (1.6)	4.2 (1.5)	4.7 (1.7)
Stage (%)			
I	26.9	26.9	26.9
II	62.7	63.1	62.1
III	10.4	10.0	11.0
ECOG performance status (%)			
0	89.1	88.9	89.4
1+	10.9	11.1	10.6
Chemotherapy regimen (%)			
AC	86.2	96.1	72.7
CMF	11.9	2.5	24.6
CAF	1.3	1.4	1.1
A-CMF	0.6	0.0	1.6

SD: Standard deviation; ANC: absolute neutrophil count; ECOG: Eastern Cooperative Oncology Group; AC: doxorubicin plus cyclophosphamide; CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; CAF: cyclophosphamide, doxorubicin, and 5-fluorouracil; A-CMF: doxorubicin followed by cyclophosphamide, methotrexate, and 5-fluorouracil.

TABLE 2
Comparison of Outcomes between Patients in the Low-Risk and High-Risk Groups

Outcome	Overall	Low-risk group	High-risk group
Planned dose received on time ≤85% (%)	5.0	4.2	5.6
Hospitalization due to febrile neutropenia (%)	2.9	0.8	4.4
Febrile neutropenia (%)	7.5	2.6	11.1
Totals, *n*, (%)	624	264 (42.3)	360 (57.7)

Study Endpoints

Study endpoint incidence by risk group is reported in Table 2. The rates of hospitalization because of febrile neutropenia and an episode of febrile neutropenia in the low-risk group were very low: 0.8% (95% confidence interval [95% CI],: -0.3–1.9%) and 2.6% (95% CI, 0.7–4.5%), respectively. The majority of low-risk and high-risk patients (95.8% vs. 94.4%, respectively) received > 85% of their planned dose on time. The dose intensities delivered to the low-risk and high-risk groups were high relative to planned dose, with no significant difference between groups ($P = 0.547$). Planned chemotherapy dose intensity for over 92% of the patients overall (and historic-control patients) was > 85% of the standard referenced dose intensity. Therefore, study and control patients overall received regimens, doses, and timing considered standard by the oncology community.

TABLE 3
Matched Pairs Analysis

Outcome	Odds ratio	*P* value
Planned dose received on time ≤85%	2.6	0.001
Hospitalization due to febrile neutropenia	1.1	0.724
Febrile neutropenia	0.9	0.541
Totals, pairs	$n = 358$[a]	

[a] Two high-risk study patients were missing one of the matching variables.

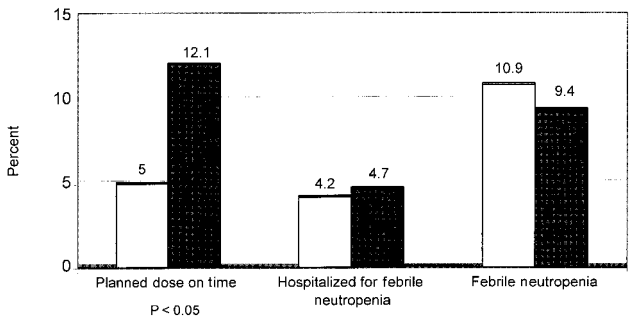

FIGURE 1. Comparison of outcome incidence between study patients and historic-matched control patients. The planned dose was received on time ($P < 0.05$). Open boxes: high-risk patients ($n = 358$); solid boxes: historic-matched control patients ($n = 358$). The numbers on top of the bars indicate the percentage of patients with an event. Only 358 pairs were created.

Matched-Pairs Analysis

The geographic distribution of patients in the historic-control group was 26.3% (Northeast), 37.2% (Midwest), 13.8% (South), and 22.7% (West), which is similar to that of the study patients (30.6%, 34.0%, 19.5%, and 15.9%, respectively). On average, matched pairs differed with regard to baseline ANC by only 0.406 $\times 10^9$/L and in age by < 1 year. Two high-risk study patients remained unmatched because of a missing value in a matching variable. Estimated from the 358 matched pairs, a historic-control patient was 2.6 times more likely to receive ≤ 85% of the planned dose of chemotherapy on time, compared with a matched high-risk study patient ($P = 0.001$). Odds ratios for hospitalization because of febrile neutropenia and an episode of febrile neutropenia were 1.1 ($P = 0.724$) and 0.9 ($P = 0.541$), respectively, times higher than a matched high-risk study patient (Table 3). The incidence of the endpoints in the two matched samples

are presented in Figure 1. The rate of low delivered dose intensity for the high-risk patients was 5.0% compared with 12.1% in the historic matched control patients. The incidences of hospitalization because of febrile neutropenia and febrile neutropenia were similar (4.2% vs. 4.7% and 10.9% vs. 9.4%) for the high-risk and historic-control patients, respectively. Note the slight differences in the high-risk group because of two unmatched patients (Table 2).

DISCUSSION

To our knowledge, the current prospective study is the first to demonstrate that filgrastim support targeted to patients identified as being at high risk for neutropenic complications based on first-cycle ANC nadir is feasible and may improve the delivery of planned chemotherapy dose on time without increasing febrile neutropenia-related morbidity and hospitalization. Discrimination of patients was successful, resulting in low false-negative rates. The risk model strategy also resulted in 95% of patients receiving $>$ 85% of their planned dose of chemotherapy on time. Several retrospective studies[16–18] have identified first-cycle nadir ANC as a reliable predictor of neutropenic complications; however, the specific cutoff point for allocating patients to high-risk and low-risk groups must be identified for each chemotherapy regimen. For example, the study by Silber et al. demonstrated that for patients primarily receiving CMF chemotherapy, the ANC cutoff point identifying the 50% of patients most at risk was 1.0×10^9/L.[16] In the current prospective study, it was anticipated that the majority of patients would receive AC chemotherapy. An ANC cutoff point of 0.5×10^9/L was selected to ensure that patients with NCI Grade 4 neutropenia, who are at increased risk for febrile neutropenia and dose modifications, would be treated prophylactically with filgrastim. The current study results indicate that using a cutoff of 0.5×10^9/L successfully allocated the 50% of patients most at risk for neutropenic complications to the high-risk group. The targeted filgrastim strategy can be applied using other cutoff points. Silber et al. have investigated the economic rational for choosing a particular cutoff point.[19]

A practical difficulty of the current study is that nadir ANC is not routinely collected in clinical practice. This study required two to three nadir ANC measurements to classify patients into high-risk and low-risk groups. Forty-eight study patients (7%) did not have an ANC nadir recorded and were declared ineligible. For the majority of study patients, the necessary laboratory blood draws were obtained, demonstrating the feasibility of obtaining nadir ANC. We also observed that the baseline ANC comparisons between the high-risk group and the low-risk group reflect a possible relation between low baseline ANC and low first-cycle nadir ANC. Risk-related prophylactic filgrastim support may be easier to implement in the clinical setting if the ANC nadir count in the risk model is substituted with the ANC obtained on Day 1 of Cycle 2. In the trial data, the estimated Pearson correlation coefficient (r) between the Cycle 1 nadir ANC and the Cycle 2 baseline ANC was low and insignificant ($r = 0.05$; $P = 0.255$). Further research is needed to model the relation between the ANC of Day 1 of Cycle 2 and the first-cycle ANC nadir. It is interesting to note that age, disease stage, and performance status did not appear to differ between the high-risk and low-risk groups.

The requirement that the rate of febrile neutropenia be zero in the group of patients at low risk of developing neutropenic complications is idealistic. It could be obtained if the assignment rule to low-risk and high-risk groups was perfect. The observed incidence of febrile neutropenia in the low-risk group (2.6%) was minimal and appears to support the conclusion that the type I error is tolerable.

The current study has several limitations. This model does not help patients who are at risk of neutropenic complications during the first cycle of chemotherapy. Further research efforts need to be directed toward the identification of the predictors of first-cycle febrile neutropenia. The study design limits our ability to ascertain the effect of withholding filgrastim from patients who are at high risk of developing neutropenic complications because we did not conduct a randomized trial of the effect of targeted filgrastim use. In particular, the incidence of hospitalization because of febrile neutropenia and the delivered dose intensity may have been affected in favor of the treatment because of the trial setting in which the patients were treated. It is possible that study patients are more likely to receive outpatient treatment for febrile neutropenia, resulting in less febrile neutropenia hospitalizations than reported in the current study. Furthermore, the chemotherapy dose delivered in the current study might have been affected by the fact that oncologists knew that planned dose of chemotherapy on time was a recorded outcome. As such, the physicians may have been more aggressive in the delivery of chemotherapy than under normal conditions. If this is the case, the study indicates that with risk-related prophylactic filgrastim support, a more aggressive treatment regimen is feasible.

We have tried previously to estimate the effect of this strategy on the high-risk patients by using a matched-pair analysis with a historic-control group as a second-best, bias-control alternative to a random-

ized trial to assess the risk of a randomized trial. In any event, the matched pairs analysis was not intended to provide conclusive evidence. Control patients from the same physician practices were not available and treatment practice may have changed during the control data span of 6 years. We tried to closely match patients by the known risk factors associated with the outcomes, but differences in practice pattern cannot be ruled out as a potential effect on the study results regarding case–control differences.

Conversely, the results of the matched-pairs analysis are positive despite the conservative approach taken by matching high-risk study patients to the entire control sample. Furthermore, febrile neutropenia may have been underreported in historic-control patients. Several sites reported the same number of events for febrile neutropenia hospitalization and febrile neutropenia, suggesting that febrile events not requiring hospitalization were not reported for some historic-control patients. In the current prospective study, episodes of febrile neutropenia and hospitalization for febrile neutropenia were recorded carefully. The risk of neutropenic fever and neutropenic fever requiring hospitalization was expected to be lower in the control sample than that in the high-risk study group. Therefore, the administration of filgrastim to the high-risk group not only allowed the on-time administration of chemotherapy but also lowered the risk of neutropenic fevers and hospitalizations to the low level of the control sample.

Risk-related prophylactic support with filgrastim appears to enable the allocation of healthcare resources to appropriate patients. This process may result in cost containment and appears to be an effective strategy with which to obtain the timely administration of the planned dose of chemotherapy for most patients without increasing the risk of febrile neutropenia-related hospitalization. Further research is needed to confirm the results obtained in the current study in a randomized trial, if feasible, and in other chemotherapy and disease settings.

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